TWO STABLE STEADY STATES IN THE HODGKIN-HUXLEY AXONS

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ABSTRACT Two stable steady states were found in the numerical solution of the Hodgkin-Huxley equations for the intact squid axon bathed in potassium-rich sea water with an externally applied inward current. Under the conditions the two stable steady-states exist, the Hodgkin-Huxley equations have a complex bifurcation structure including, in addition to the two stable steady-states, a stable limit cycle, two unstable equilibrium points, and one asymptotically stable equilibrium point. It was also concluded that two stable steady states can appear in the Hodgkin-Huxley axons when the leak current is comparable to the currents through the Na and K channels.

It has been recognized that the Hodgkin-Huxley equations (Hodgkin and Huxley, 1952) provide a good phenomenological description of nerve excitation. The equations have been particularly useful in clarifying the time-dependent behavior of nerve excitation (Cole, 1972; Aihara and Matsumoto, 1982). It has been understood that under the various conditions so far tested, the Hodgkin-Huxley equations have stable solutions with an asymptotically stable equilibrium point and/or a stable limit cycle (Hassard, 1978; Aihara and Matsumoto, 1982) but not with multiple stable equilibrium points. Here we report that the equations have steady-state solutions with two stable equilibrium points when the steady inward current is externally applied to the axon bathed in a potassium-rich medium.

GLOSSARY

I	membrane current density, positive outward (μA/cm^2)
V	membrane potential difference, inside relative to outside (mV)
m	sodium activation (dimensionless, varying between 0 and 1)
h	sodium inactivation (dimensionless, varying between 0 and 1)
n	potassium activation (dimensionless, varying between 0 and 1)
t	time (ms)
C	membrane capacity = 1 μF/cm^2
V_{Na}, V_K, V_L	reversal potentials for sodium, potassium and leakage current components, respectively (all in mV)
$\bar{g}_{Na}$, $\bar{g}_K$, $\bar{g}_L$	maximal ionic conductances, through sodium, potassium and leakage current components, respectively (all in mS/cm^2)
T	temperature (°C).

The Hodgkin-Huxley equations are

$$\frac{dV}{dt} = [I - \bar{g}_{Na} \cdot m^3h(V - V_{Na}) - \bar{g}_K \cdot n^4(V - V_k) - \bar{g}_L \cdot (V - V_L)]/C, \quad (1)$$

$$\frac{dm}{dt} = \phi[(1 - m) \cdot \alpha_m(V + \Delta V) - m \cdot \beta_m(V + \Delta V)], \quad (2)$$

$$\frac{dh}{dt} = \phi[(1 - h) \cdot \alpha_h(V + \Delta V) - h \cdot \beta_h(V + \Delta V)], \quad (3)$$

$$\frac{dn}{dt} = \phi[(1 - n) \cdot \alpha_n(V + \Delta V) - n \cdot \beta_n(V + \Delta V)]. \quad (4)$$

In Eqs. 1–4, $\phi = 3^{(T-6.3)/10}$ and $\Delta V = -9.32 \times \ln([Ca]_{eff}/41.8)$ (mV). The effective calcium concentration $[Ca]_{eff}$ (mM) can be expressed in terms of the external Ca and Mg ion concentrations, [Ca] and [Mg], as $[Ca]_{eff} = [Ca] + (3/5)[Mg]$, according to Frankenhaeuser and Hodgkin (1957). In the above equations, the values of $\bar{g}_{Na}$, $\bar{g}_K$, $\bar{g}_L$, V_L, C, and T are fixed at 120.0, 36.0, 0.3 mS/cm^2, −24.3 mV, 1.0 μF/cm^2, and 18.0°C, respectively. We consider the intact axon of squid externally surrounded by a potassium-rich medium. Thus, the internal Na and K ion concentrations are kept constant at 50.0 and 400.0 mM, respectively. The external medium is a mixture of natural sea water (NSW) and an aqueous solution of 550 mM KCl, so that the concentrations of external Na, K, Ca, and Mg ions are determined by the mixing ratio of NSW to 550 mM KCl. As NSW contains 460 mM Na, 10 mM K, 10 mM Ca, and 53 mM Mg ions (Hodgkin, 1964), the concentrations of

these ions in the external medium of the mixture of NSW and 550 mM KCl are represented by the external K ion concentration [K] as follows:

$$[\mathrm{Na}] = \frac{23}{27}(550 - [\mathrm{K}]),$$

$$[\mathrm{Ca}] = \frac{1}{54}(550 - [\mathrm{K}]), \qquad [\mathrm{mM}] \qquad (5)$$

$$[\mathrm{Mg}] = \frac{53}{540}(550 - [\mathrm{K}]).$$

The equilibrium potentials of V_{Na} and V_K are calculated with the Nernst equation (Hodgkin, 1964), using the above internal and external ion concentrations. Also the value of ΔV in Eqs. 1–4 can be obtained. The stability of the steady-state solutions was judged from examining the eigenvalues of the Jacobian matrix corresponding to the solutions (Aihara and Matsumoto, 1982).

The Hodgkin-Huxley Eqs. 1–4 were numerically solved by using a HITAC-M200H computer (Hitachi Co., Ltd., Tokyo) at the University of Tokyo Computer Centre. Fig. 1 shows a set of steady membrane potentials corresponding to steady-state solutions when $I = 0$. In this case, the Hodgkin-Huxley equations have a steady state of an asymptotically stable or unstable equilibrium point and/or a stable limit cycle, depending on the external K concentration [K]. With [K] > 58.5 mM or [K] < 29.8 mM, there is a unique steady state with an asymptotically stable point (thick solid portion of the line in Fig. 1). In the range of 29.8 mM < [K] < 58.5 mM, the equations have a steady state with an unstable point (broken portion of the line) and a stable limit cycle. In the figure, the maximal and minimal membrane potentials of the limit cycle are represented as thin solid lines. The stable limit cycle bifurcates at the external [K] = 58.5 mM to the lower K concentration range. In the range of 22.8 mM <[K] < 29.8 mM, the stable limit cycle and the asymptotically stable equilibrium point coexist. The stable limit cycle suddenly disappears at the external [K]-22.8 mM. The disappearance is due to the coalescence with another unstable limit cycle, as usually observed in the Hodgkin-Huxley systems (Hassard, 1978; Aihara and Matsumoto, 1982). The period of the limit cycle decreases monotonically as [K] increases; it is 6.9 ms for [K] = 22.8 mM and 3.1 ms when [K] = 58.5 mM.

On the other hand, it was found that the Hodgkin-Huxley equations can have multiple steady states when an inward current with an amplitude exceeding a critical value is externally applied to the axon. This characteristic is summarized in Fig. 2 as a bifurcation diagram with $I = -20.0\ \mu\mathrm{A/cm^2}$. The S-shaped curve in Fig. 2 shows a set of the steady membrane potentials in the Hodgkin-Huxley equations. The heavy solid and broken portions of the curve represent the asymptotically stable and unstable equilibrium points, respectively. The values of [K] at *B*–*F* are 417.0, 51.8, 52.1, 66.0, and 152.9 mM, respectively. The equilibrium points between *A* and *B* and between *F* and *G* are stable nodes. The equilibrium points from *B* to *D* have four real eigenvalues, at least one of which is positive. The number of the positive real eigenvalues, or the dimension of the unstable manifold of the equilibrium point, is one between *B* and *C* and two between *C* and *D*, respectively. The equilibrium points between *D* and *F* have complex conjugate dominant eigenvalues. The real part of the complex conjugate eigenvalues is positive between *D* and *E* and negative between *E* and *F*, respectively. The point *E* is a normal Hopf bifurcation point (Marsden and McCracken, 1976). The stable limit cycle bifurcates at *E* to the lower K concentration range and vanishes around

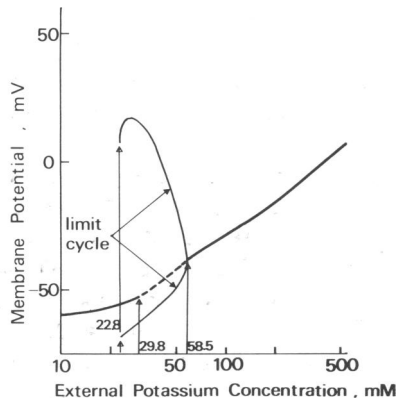

FIGURE 1 Relationship between the steady membrane potential (ordinate) and the external K concentration [K] (abscissa) with $I = 0$. The heavy solid and broken curves represent stable and unstable equilibrium points, respectively. The thin solid curves bifurcating at the external [K] = 58.5 mM to the lower K concentration range denote maximum and minimum membrane potentials of the wave forms of a stable limit cycle.

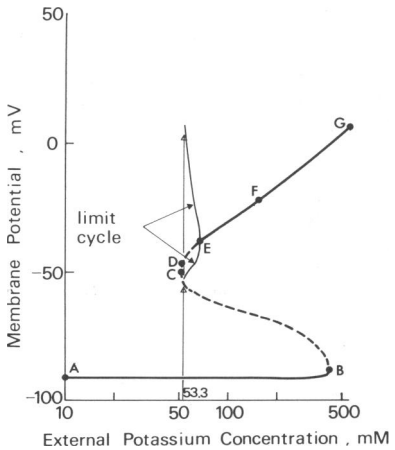

FIGURE 2 A bifurcation diagram of the Hodgkin-Huxley equations with $I = -20.0\ \mu\mathrm{A/cm^2}$. The ordinate and the abscissa are the membrane potential and the external K concentration [K], respectively. The S-shaped curve shows the set of the steady membrane potentials corresponding to the equilibrium points in the Hodgkin-Huxley equations. The heavy solid and broken curves represent stable and unstable equilibrium points, respectively. The thin solid curves bifurcating at *E* to the lower K concentration range denote the maximum and minimum membrane potentials at the stable limit cycle.

[K] = 53.3 mM (Fig. 2); two thin solid lines in the figure represent the maximum and minimum membrane potentials of the wave form. The period of the limit cycle decreases monotonically as [K] increases, from 10.8 ms ([K] = 53.3 mM) to 3.4 ms ([K] = 66.0 mM). The stable limit cycle does not disappear at the point C but at the external K concentration of 53.3 mM, which is located between D and E in Fig. 2. This indicates that the limit cycle does not disappear by a kind of the saddle-node bifurcation or Ω-explosion (Zeeman, 1982). The following three mechanisms are possible to explain the disappearance: (*a*) coalescence with an unstable limit cycle, (*b*) secondary bifurcation of the stable limit cycle, and (*c*) saddle-connection catastrophe through a homoclinic orbit (Zeeman, 1982; Andronov et al., 1973).

In the range of [K] from 66.0 mM < [K] < 417.0 mM (*E–B*), the Hodgkin-Huxley equations have two asymptotically stable equilibrium points. The range of [K] where the Hodgkin-Huxley equations have two asymptotically stable equilibrium points becomes wider with the increase of the absolute value of the inward-flowing steady current I. In the case of $I = -30\ \mu A/cm^2$, the range of [K] for the two stable states is between 70.0 and 545.7 mM. This can be related to generation of long-lasting action potentials and hyperpolarizing responses of membrane potentials in squid giant axons bathed in K-rich medium with an applied steady inward current (Segal, 1958; Moore, 1959; Tasaki, 1959). It is noted that two stable steady states can also be formed by changing V_L even if no external current is applied. This is easily understood when we consider that the effect of the steady external current I is mathematically equivalent to a change of the leak current; that is, I of $-20\ \mu A/cm^2$ corresponds exactly with replacing V_L by $V_L - 20/\bar{g}_L$. This may explain the formation of two stable steady states in squid giant axons internally perfused with solutions containing low concentrations of Na or Cs and, at the same time, bathed in media containing high concentration of $CaCl_2$ (Tasaki et al., 1969; Watanabe, 1972; Meves and Vogel, 1973; Inoue, 1980). Under these bi-ionic conditions, the contribution of the leak current is comparable to the currents through the sodium and potassium channels. Then, phenomena similar to those considered in this report occur in axons under conditions far from physiological ones. Comparison between the two stable steady states experimentally observed in squid axons under various conditions and those following from the Hodgkin-Huxley equations will be described in detail elsewhere.

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